REMARKS

Status of Claims

Claims 1-13 are pending in the application and are under examination. Claims 14-16 are camceled.

Claim 1 has been amended in response to the Examiner's comments under "Claim Interpretation."

Claim Interpretation

According to the Examiner in paragraphs 4 and 5 of the Office Action, the term "characteristic kinetic quantity of a chemical reaction" has not been defined by Applicants, therefore it is interpreted as any measurable variable. Further, the term "species including at least one fluorophore" is interpreted as any molecule which comprises at least one fluorophore, involved in any chemical reaction.

In response, Applicants

- herewith amend claim 1 for greater precision and clarity, as supported by the Abstract and paragraphs [0011]-[0018] of the specification and as further explained in greater detail below, and in direct response to the requirements and suggestions of the Examiner, and
- respond to the current rejections in view of the amended claim 1.

It is respectfully submitted that the refinement of claim 1 is in response to the suggestions of the Examiner and advances prosecution of the application, thus entry at this stage in prosecution is respectfully requested.

Examiner's Response to Arguments

The rejection under 35 USC 112, second paragraph, is withdrawn. The Examiner however maintains the remaining rejections of record for reasons of record.

Regarding the rejection of claims 1-13 under 35 U.S.C. §112, first paragraph, enablement, the Examiner appreciates the extensive review of FRET literature; however, the FRET

measurement is not an issue in the enablement rejection. The issues, as detailed in the rejection are:

i) Lack of evidence (either in the disclosure or in the prior art) that in **any** chemical reaction a concentration of reactants can be perturbed by impinging light on the reaction. There is no evidence that merely illuminating the reaction with a light which enables observation of the FRET effect between fluorescent donor and acceptor has any effect on the kinetics of hybridization of the two nucleic acids. The fact that light stimulates a population of fluorescent acceptors bound to DNA has no bearing on the DNA hybridization kinetics. The only molecules that might be subject to perturbation of their concentrations by light are fluorophores themselves.

ii) Lack of evidence of how any "kinetic quantity" can be derived from such a measurement.

According to the Examiner, none of the references cited by Applicants provide evidence that using light to observe FRET effects in biological systems causes perturbation of reactant concentrations and can be used to measure "kinetic quantities" in such reactions. Finally, Applicants' statement that the method relies on "an inversion of the principles of application of conventional measurements of relaxation kinetics" is not backed up with any evidence that such principle actually works as claimed.

Applicants respectfully traverse.

Before discussing the objections it will be necessary to explain what the invention, as defined particularly in amended claim 1, is about and how it works. Perhaps the previous "European structure" of claim 1 led the Examiner to a broader interpretation of the invention than Applicants had intended. Claim 1 has been carefully reviewed and revised to more clearly and concretely define the invention.

In particular, there is no "magic" change of concentrations by purely having light impinge on the sample. Rather, generation of a non-equilibrium state is a consequence of the special choice of reactants, namely a first reactant comprising a FRET-acceptor, a second reactant comprising a FRET-donor, a product of the chemical (balance) reaction comprising a complex of said reactants, and the FRET-acceptor being a photochrome. These are the important elements of

the invention. If you have such a sample in solution, the chemical reaction finds its equilibrium according to the intensive thermodynamic parameters and the absolute amounts of reactants. As one skilled in the art knows, the equilibrium is the state in which the concentrations of the reactants and the products do not change any longer. Thus, the non-equilibrium state is implicitly defined as any state not being the equilibrium state.

In order to carry out the measurement according to the invention one has to have light of a wavelength suitable to switch the photochromic state of the FRET-acceptor impinge on the sample. Hereby the photochromic state of the acceptor is switched in the free ligand as well as in the complex (product). As thoroughly explained in the application (see e.g. paragraph [0016], [0039] and [046] of the specification as published), the return to the unswitched photochromic state is much slower in the ligand than in the complex, due to a FRET-dependent de-excitation channel. Thus, switching of the photochromic state is less efficient in the product than in the free ligand. That is, the concentration of the species "unswitched ligand " is changed in a different way than the concentration of the species "unswitched complex" is changed. Thus, the reaction "unswitched ligands to unswitched complex" is no longer in equilibrium. The return to the equilibrium can be observed by FRET-dependent fluorescence, because FRET-efficiency is different in unswitched complex and switched complex (different overlap of spectra of donor and acceptor).

This is straight forward physical chemistry. There is no need to give examples in literature, that concentrations can be changed by illuminating the sample as requested by the Examiner.

Regarding the rejection of claims 1-3 and 7-13 under 35 U.S.C. 102(b) as anticipated by Giordano et al., the Examiner summarizes Applicants arguments as follows:

Giordano et al. do not teach generating a non-equilibrium state of a chemical reaction and observing by means of a fluorescence signal, at least one portion of a relaxation of concentrations of the species involved.

In response to Applicants' position, the Examiner takes the position that Applicants, in their response, did not define the terms "non-equilibrium state", therefore, any state of the reaction can be considered to be "non-equilibrium". Giordano et al. clearly observe the non-equilibrium state of the conversion between the two forms of the diheteroarylethenes, as shown in Fig. 4. Therefore Giordano et al. explicitly teach the claimed method.

In response, Applicants now refer the Examiner to the revised claim 1.

Giordano et al. disclose FRET-pairs, in which the FRET-acceptor is a chromophore. The invention of Giordano et al. offers a method that makes use of such molecules for determining rate constants of chemical reactions.

It is however not true that Giordano et al. disclose the method according to the present invention. Giordano et al. do not disclose the chemical (balance) reaction. Rather they ***synthesize a molecule irreversibly*** consisting of the FRET-Donor and the FRET-acceptor. All they do is switch the acceptor on and off and detected the FRET-dependent fluorescence, which is different in the switched-on state and the switched-off state.

Giordano et. al. give no hint to providing a first ligand comprising the acceptor and a second ligand comprising the donor, both ligands taking part in a (balance) reaction yielding a complex of both ligands, FRET only occurring in the complex but not between the free ligands.

Thus, it can only be concluded that the present invention is novel over Giordano et al. and based on an inventive step.

Further, there is no lack of evidence or disclosure in the application. Rather, all necessities of the invention are disclosed in the specification (first ligand with acceptor, second with donor, balance reaction yielding a complex of first and second ligands, acceptor being a photochrome, sample being illuminated by "switching" light) and the physical-chemical mechanism is thoroughly explained.

Accordingly, withdrawal of the rejection is respectfully requested.

Regarding the rejection of claims 4-6 under 35 U.S.C. §103(a) as obvious over Giordano et al. and Watrob et al., Applicants previously argued that these claims are allowable by virtue of their dependency from allowable claim 1.

Applicants maintain their position.

Claim Rejections - 35 USC § 112

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, ***while being enabling*** for monitoring chemical reactions in which the chemical species are fluorophores themselves and in which the physical or chemical properties of the fluorophores are changed upon irradiation with light in such a way as to create populations of molecules in two different states where the populations of molecules are different from the populations before the irradiation, does not reasonably provide enablement for monitoring chemical reactions with any molecule having a fluorophore attached to it in any other chemical reaction. According to the Examiner, there is no support in the specification and prior art for the full scope of the claimed method. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

In response, Applicants refer the Examiner to the revised, more precise claim 1. It is respectfully submitted that the specification is enabling for claim 1 as revised to more succinctly and less ambiguously define the invention.

There is no lack of evidence or disclosure in the application. Rather, all necessities of the invention are disclosed in the specification (first ligand with acceptor, second with donor, balance reaction yielding a complex of first and second ligands, acceptor being a photochrome, sample being illuminated by "switching" light) and the physical-chemical mechanism is thoroughly explained. This is straight forward physical chemistry. There is no need to give examples in literature, that concentrations can be changed by illuminating the sample as requested by the Examiner.

Accordingly, withdrawal of the rejection is respectfully requested.

According to the Examiner, the specification has no working examples and no examples of how to determine kinetic parameters of any other reaction in which molecules are labeled with fluorophores.

In response, Applicants submit that no examples are required where the chemistry is explained to the extent that the invention can be practiced without undue experimentation by those of ordinary skill in the art.

The Court in *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

It is explained in In re Wands, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, all factors (A)-(H) must be taken into consideration in determining enablement. The Court cautioned that it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

Applicants respectfully submit that the specification, at the time the application was filed, would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. Applicants would be pleased to present a Declaration from an expert in this field if such would advance prosecution of this application. If the Examiner would agree that such a Declaration might be persuasive on one or more of the above factors, Applicants would like to conduct a telephone interview with the Examiner to discuss the general content of the Declaration.

Those working in this art would not consider any possible experimentation involved in testing to be ***unreasonable***. It has been held that, in certain art, "reasonable experimentation" may be time consuming and expensive. In *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989), the court reversed the

findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of ***time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation***. In the present art, in contrast, the level of predictability is high, and with the teaching of the present specification in hand, those of ordinary skill are well positioned to practice the present invention without any undue experimentation.

Further, the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since ***a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.***'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

Thus, the Examiner has not established that undue experimentation is needed in the practice of the present invention.

The specification provides no evidence that the disclosed use of photochromic FRET acceptor molecules provides means for detecting any kinetic quantity of a chemical reaction, for example, a rate constant. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. Applicants did not show that light can cause deviation from equilibrium

concentrations of any chemical species in any chemical reaction in which the products are labeled with photochromic acceptors, except the photochromic acceptors themselves.

In response Applicants refer to the revised, more precise claim 1, and

The unpredictability of the art and the state of the prior art

According to the Examiner, the only example found in literature for use in deteitnining reaction rates is Giordano et al. (J. Am. Chem. Soc., vol. 124, pp. 7481-7489, 2002; cited in the IDS), in which the photoconversion rates of diheteroarylethene compounds bound to Lucifer Yellow cadaverine were determined using light-induced conversion of diheteroarylethene between two different states, open and closed.

In response, Applicants submit that the position of the Examiner is based on a misunderstanding of the chemistry involved in the present invention. The chemistry has been explained above. As also explained above, Giordano et al. disclose FRET-pairs, in which the FRET-acceptor is a chromophore. The invention of Giordano et al. offers a method that makes use of such molecules for determining rate constants of chemical reactions.

It is however not true that Giordano et al. disclose the method according to the present invention. Giordano et al. do not disclose the chemical (balance) reaction. Rather they ***synthesize a molecule irreversibly*** consisting of the FRET-Donor and the FRET-acceptor. All they do is switch the acceptor on and off and detected the FRET-dependent fluorescence, which is different in the switched-on state and the switched-off state.

Giordano et. al. give no hint to providing a first ligand comprising the acceptor and a second ligand comprising the donor, both ligands taking part in a (balance) reaction yielding a complex of both ligands, FRET only occurring in the complex but not between the free ligands.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to detection of kinetic parameters of any chemical reaction in which participating molecules are labeled with fluorescent acceptor and donor molecules, including determining which molecules aside from the

photochromes themselves undergo physical or chemical changes in the presence of light of any wavelength, and how such kinetic constants can be determined This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Applicants in response submit the chemistry, contrary to the position of the Examiner, is straight-forward and well within the skill of the person of ordinary skill to practice, given the teaching of the present specification.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Applicants agree.

Claim Rejections - 35 USC § 102

The Examiner repeats the rejection of record.

Applicants have responded to the rejection by responding to the revised position of the Examiner as set forth in the above Examiner's Response to Applicants' Arguments.

Claim Rejections - 35 USC § 103

The Examiner repeats the rejection of record.

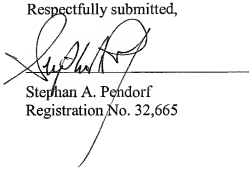
Applicants have responded to the rejection by responding to the revised position of the Examiner as set forth in the above Examiner's Response to Applicants' Arguments.

Accordingly, withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account Number 16-0877.

Favorable consideration and early issuance of the Notice of Allowance are respectfully requested. **Should further issues remain prior to allowance, the Examiner is respectfully requested to contact the undersigned at the indicated telephone number.**

Respectfully submitted,



Stephan A. Pendorf
Registration No. 32,665

Patent Central LLC
1401 Hollywood Blvd.
Hollywood, FL 33020-5237
(954) 922-7315

Date: **September 8, 2009**